

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

Claim 1. (Presently Amended) A method of treating or ameliorating hypertension ~~an indication of the invention~~ in an animal, including a human, comprising administering an effective amount of (A) a compound of the formula I:



wherein:

a. Het is a five ~~or six~~-membered heterocycle having a ~~first~~ one ring nitrogen and ~~optionally, a second or third ring nitrogen, with the remaining ring atoms being carbon, one ring oxygen, or sulfur; provided that Het wherein said Het is an isoxazole and~~ is not thiazole, imidazole, oxazole, or a dihydro or tetrahydro analogs thereof;

b. Het can be substituted on carbon atoms with

1. one or more substituents independently selected from hydrogen, acylamino, acyloxyalkyl, alkanoyl, alkanoylalkyl, alkenyl, alkoxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylamino, (C₁-C₃)alkylenedioxy, allyl, amino, ω-alkylenesulfonic acid, carbamoyl, carboxy, carboxyalkyl (which alkyl can be substituted with alkyloxyimino), cycloalkyl, dialkylamino, halo, hydroxy, (C₂-C₆)hydroxyalkyl, mercapto, nitro, sulfamoyl, sulfonic acid, alkylthio, alkylsulfonyl, alkylsulfinyl, alkylsulfonamido, trifluoromethyl, morpholin-4-yl, 4-[C₆ or C₁₀]aryl]piperidin-1-yl, 4-[C₆ or C₁₀]aryl]piperazin-1-yl, thiomorpholin-4-yl, piperidin-1-yl, Ar* {wherein, consistent with the rules of aromaticity, Ar* is C₆ or C₁₀ aryl or a 5- or 6-membered heteroaryl ring, wherein the 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N, each heteroaryl ring can be optionally fused to a substituted benzene, pyridine, pyrimidine, pyridazine, pyrazine, or (1,2,3)triazine (wherein the ring fusion is at a carbon-carbon double bond of Het)}, Ar*-alkyl, Ar*-O, Ar*SO₂-, Ar*SO-, Ar*S-, Ar*SO₂NH-, Ar*NH, (N-Ar*)(N-alkyl)N-, Ar*C(O)-, Ar*C(O)NH-, Ar*NH-C(O)-, and (N-Ar*)(N-alkyl)N-C(O)-; or

2. two adjacent substitutions together with their ring carbons form a fused C₆ or C₁₀ aryl ring which aryl ring can be substituted as set forth below; or

3. two adjacent substitutions together with their ring carbons form a C₅-C₇ fused cycloalkyl ring having up to two double bonds including any fused double bond of the Het group, which cycloalkyl ring can be substituted by one or more of the group consisting of alkyl, alkoxycarbonyl, amino, aminocarbonyl, carboxy, fluoro, or oxo; or
 4. two adjacent substitutions together with their ring carbons form a fused 5- or 6-membered heteroaryl ring, wherein the 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N; or
 5. two adjacent substitutions together with their ring carbons form a fused five to eight membered fused heterocycle, wherein the ring fusion is at a carbon-carbon bond of Het, wherein the fused heterocycle consists of ring atoms selected from the group consisting of carbon, nitrogen, oxygen, sulfur, or S(O)_n, wherein S(O)_n is 1 or 2; and
- c. Het can be substituted on the ring nitrogen atoms with
1. hydrogen, alkyl, alkoxycarbonylalkyl-, Ar*, Ar*alkyl-, Ar*C(O)alkyl-, ArS*(O)alkyl-, Ar*S(O)₂alkyl-, so long as the ring nitrogen atoms are not quaternized;
 2. amino; or
 3. at most one nitrogen with oxido (-O⁻) to form an N-oxide; and
- d. Y is substituted on a ring carbon adjacent to the ~~first or second~~ ring nitrogens and is
- ~~1. hydrogen, oxo, alkyl, mercapto, alkylthio, amino, amino(C₁-C₃)alkyl, or aminophenyl, wherein the amino of the latter three groups can be (a) substituted with~~
- ~~(a) — Ar*,~~
- ~~(b) — Ar* Z, Ar* alkyl Z, Ar* Z alkyl, Ar* amino Z, Ar* aminoalkyl Z or Ar* oxyalkyl Z, wherein Z is a carbonyl or S(O)₂ or~~
- ~~(c) — formyl or alkanoyl;~~
- ~~2. — NHC(O)(CH₂)_n D R^e R^f, wherein D is oxygen, sulfur or nitrogen, wherein when D is nitrogen n is 0, 1 or 2, but when D is oxygen or sulfur n=1 or 2, and R^f is present only when D is nitrogen, wherein~~
- ~~(a) — R^e is~~
- ~~(1) — Ar*, or~~
- ~~(2) — a group of the formula Het^δ-~~
- ~~wherein Het^δ is independently the same as Het, or~~

- (3) ~~a C₃-C₈ cycloalkyl ring having up to one double bond with the proviso that the carbon linking the cycloalkyl ring to D is saturated, which cycloalkyl ring can be substituted by one or more alkyl, alkoxycarbonyl, amino, aminocarbonyl, carboxy, fluoro, or oxo substituents, or~~
(4) ~~hydrogen, (C₂-C₆)hydroxyalkyl, alkanoylalkyl, alkyl, alkoxycarbonylalkyl, alkenyl, carboxyalkyl (which alkyl can be substituted with alkoxyimino), alkoxycarbonyl, Ar*, or Ar*-alkyl; and~~
(b) ~~R^f is independently hydrogen, hydroxy(C₂-C₆)alkyl, alkanoylalkyl, alkyl, alkoxycarbonylalkyl, alkenyl, carboxyalkyl (which alkyl can be substituted with alkyloxyimino), alkoxycarbonyl, independently a group Ar* or Ar*-alkyl;~~

wherein aryl or Ar* in addition to any substitutions specifically noted can be substituted with one or more substituents selected from the group of acylamino, acyloxyalkyl, alkanoyl, alkanoylalkyl, alkenyl, alkoxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylamino, (C₁-C₃)alkylenedioxy, alkylsulfonyl, alkylsulfinyl, ω -alkylenesulfonic acid, alkylthio, allyl, amino, Ar*C(O)-, Ar*C(O)NH-, carboxy, carboxyalkyl, cycloalkyl, dialkylamino, halo, trifluoromethyl, hydroxy, (C₂-C₆)hydroxyalkyl, mercapto, nitro, morpholin-4-yl, thiomorpholin-4-yl, piperidin-1-yl, Ar*O-, Ar*-, Ar*-alkyl-, sulfamoyl, sulfonic acid, 1-pyrrolidinyl, 4-[C₆ or C₁₀]arylpiperidin-1-yl and 4-[C₆ or C₁₀]arylpiperazin-1-yl; and

heterocycles except those of Het or Ar*, can be substituted with, in addition to substitutions specifically noted, one or more substituents selected from acylamino, alkanoyl, alkoxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylamino, alkylsulfonyl, alkylsulfinyl, alkylthio, amino, Ar*C(O)-, Ar*O-, Ar*-, Ar*-alkyl, carboxy, dialkylamino, fluoro, fluoroalkyl, difluoroalkyl, hydroxy, mercapto, 4-[C₆ or C₁₀]arylpiperidin-1-yl, 4-[C₆ or C₁₀]arylpiperazin-1-yl, (C₁-C₃)alkylenedioxy, oxo, sulfamoyl, and trifluoromethyl;

or a pharmaceutically acceptable salt of said compounds.

Claim 2. (Presently Amended) The method of claim 1, wherein

- a. Het is a five ~~or six~~-membered heterocycle having a first one ring nitrogen and ~~optionally, a second or third ring nitrogen, with the remaining ring atoms being carbon, one ring oxygen, or sulfur; provided that Het wherein said Het is an unsubstituted isoxazole is not thiazole, imidazole, oxazole, or a dihydro or tetrahydro analogs thereof;~~
b. ~~Het can be substituted on carbon atoms with~~

1. ~~one or more substituents independently selected from hydrogen, acylamino, alkanoyl, alkanoylalkyl, alkoxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylamino, amino, ω-alkylenesulfonic acid, carbamoyl, carboxy, carboxyalkyl (which alkyl can be substituted with alkyloxyimino), cycloalkyl, dialkylamino, halo, hydroxy, (C₂-C₆)hydroxyalkyl, mercapto, nitro, sulfamoyl, sulfonic acid, alkylthio, alkylsulfonyl, alkylsulfinyl, alkylsulfonamido, trifluoromethyl, morpholin-4-yl, thiomorpholin-4-yl, 4-[C₆-or C₁₀]aryl piperidin-1-yl, 4-[C₆-or C₁₀]aryl piperazin-1-yl, piperidin-1-yl, Ar* {wherein, consistent with the rules of aromaticity, Ar* is C₆-or C₁₀-aryl or a 5- or 6-membered heteroaryl ring, wherein the 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N, each heteroaryl ring can be optionally fused to a substituted benzene, pyridine, pyrimidine, pyridazine, pyrazine, or (1,2,3)triazine (wherein the ring fusion is at a carbon-carbon double bond of Het)}, Ar*-alkyl, Ar*-O, Ar*SO₂, Ar*SO, Ar*S, Ar*SO₂NH, Ar*NH, (N-Ar*)(N-alkyl)N, Ar*C(O), Ar*C(O)NH, Ar*NH-C(O), and (N-Ar*)(N-alkyl)N-C(O); or~~

2. ~~two adjacent substitutions together with their ring carbons form a fused C₆-or C₁₀-aryl ring which aryl ring can be substituted as set forth below; or~~

3. ~~two adjacent substitutions together with their ring carbons form a C₅-C₇-fused cycloalkyl ring having no double bonds except any fused double bond of the Het group, which cycloalkyl ring can be substituted by one or more of the group consisting of alkyl, alkoxycarbonyl, amino, aminocarbonyl, carboxy, fluoro, or oxo; and~~

e. ~~Het can be substituted on ring nitrogen atoms with~~

1. ~~hydrogen, alkyl, alkoxycarbonylalkyl, Ar*, Ar*-alkyl, Ar*C(O)alkyl, ArS*(O)alkyl, Ar*S(O)₂alkyl, so long as the ring nitrogen atoms are not quaternized;~~

2. ~~amino; or~~

3. ~~at most one nitrogen with oxido (-O⁻) to form an N-oxide; and~~

d. ~~Y is substituted on a ring carbon adjacent to the first or second ring nitrogens and is~~

1. ~~hydrogen, oxo, alkyl, mercapto, alkylthio, amino, amino(C₁-C₅)alkyl, or aminophenyl, wherein the amino of the latter three groups can be (a) substituted with~~

(a) ~~Ar*,~~

(b) ~~Ar*-Z, Ar*-alkyl-Z, Ar*-Z-alkyl, Ar*-aminoalkyl-Z or Ar*-oxyalkyl-Z, wherein Z is a carbonyl or S(O)₂-or~~

(c) ~~formyl or alkanoyl;~~

2. ~~—NHC(O)(CH₂)_n-D-R^eR^f, wherein D is oxygen, sulfur or nitrogen, wherein when D is nitrogen n is 0, 1 or 2, but when D is oxygen or sulfur n=1 or 2, and R^f is present only when D is nitrogen, wherein~~

~~(a) —R^e is~~

~~(1) —Ar*,~~

~~(2) —a group of the formula Het^δ-~~

~~wherein Het^δ is independently the same as Het,~~

~~(3) —a C₃-C₈ cycloalkyl ring having up to one double bond with the proviso that the carbon linking the cycloalkyl ring to D is saturated, which cycloalkyl ring can be substituted by one or more alkyl, alkoxy carbonyl, amino, aminocarbonyl, carboxy, fluoro, or oxo substituents, where multiple substituents are located on different carbon atoms of the cycloalkyl ring, except in the case of alkyl, alkoxy carbonyl, and fluoro substituents, which can be located on the same or different carbon atoms; or~~

~~(4) —hydrogen, (C₂-C₆)hydroxyalkyl, alkanoylalkyl, alkyl, alkoxy carbonylalkyl, alkenyl, carboxyalkyl (which alkyl can be substituted with alkoxyimino), alkoxy carbonyl, Ar*, or Ar* alkyl; and~~

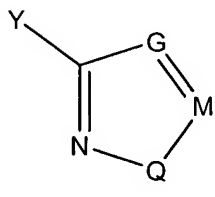
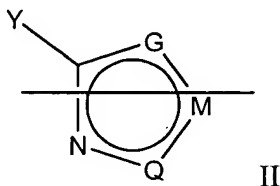
~~(b) —R^f is independently hydrogen, hydroxy(C₂-C₆)alkyl, alkanoylalkyl, alkyl, alkoxy carbonylalkyl, alkenyl, carboxyalkyl (which alkyl can be substituted with alkoxyimino), alkoxy carbonyl, independently a group Ar* or Ar* alkyl;~~

~~wherein aryl or Ar* in addition to any substitutions specifically noted can be substituted with one or more substituents selected from the group of alkyl, amino, dialkylamino, 1-pyrrolidinyl, 4-[C₆ or C₁₀]aryl piperazin-1-yl, 4-[C₆ or C₁₀]aryl piperidin-1-yl, azetidin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, piperidin-1-yl; and~~

~~heterocycles except those of Het or Ar*, can be substituted with, in addition to substitutions specifically noted, one or more substituents selected from acylamino, alkanoyl, alkoxy, alkoxy carbonyl, alkoxy carbonylalkyl, alkyl, alkylamino, alkylsulfonyl, alkylsulfinyl, alkylthio, amino, Ar*C(O), Ar*O, Ar*, Ar* alkyl, carboxy, dialkylamino, fluoro, fluoroalkyl, difluoroalkyl, hydroxy, mercapto, 4-[C₆ or C₁₀]aryl piperidin-1-yl, 4-[C₆ or C₁₀]aryl piperazin-1-yl, (C₁ or C₂)alkylenedioxy, oxo, sulfamoyl, and trifluoromethyl;~~

~~or a pharmaceutically acceptable salt thereof of said compounds.~~

Claim 3. (Presently Amended) The method of claim 1, wherein Het-Y is



wherein G, and M, ~~and~~ Q are selected from the group consisting of Θ , S, C-R^h, and C-Rⁱ, ~~and~~ N-R^g, ~~with the proviso that only one of G or Q can be O or S,~~

Q is O,

a. ~~wherein R^g is~~

~~(1) hydrogen, alkyl, alkoxyalkyl, Ar*, Ar* alkyl, Ar*C(O)alkyl, Ar*S(O)alkyl, or Ar*S(O)₂alkyl, so long as the ring nitrogen atoms are not quaternized; or~~

~~(2) amino or oxido (wherein N-R^g forms an N-oxide) and~~

b. wherein R^h or Rⁱ are

(1) independently selected from hydrogen, acylamino, ureido, thoureido, acyloxyalkyl, alkanoyl, alkanoylalkyl, alkenyl, alkoxy, alkoxyalkyl, alkoxyalkyl, alkyl, alkylamino, (C₁-C₃)alkylenedioxy, allyl, amino, ω -alkylenesulfonic acid, carbamoyl, carboxy, carboxyalkyl (which alkyl can be substituted with alkyloxyimino), cycloalkyl, dialkylamino, halo, hydroxy, (C₂-C₆)hydroxyalkyl, mercapto, nitro, sulfamoyl, sulfonic acid, alkylthio, alkylsulfonyl, alkylsulfinyl, alkylsulfonamido, trifluoromethyl, morpholin-4-yl, 4-[C₆ or C₁₀]aryl piperidin-1-yl, 4-[C₆ or C₁₀]aryl piperazin-1-yl, thiomorpholin-4-yl, piperidin-1-yl, Ar*, Ar*-alkyl, Ar*-O, Ar*SO₂-, Ar*SO-, Ar*S-, Ar*SO₂NH-, Ar*NH, (N-Ar*)(N-alkyl)N-, Ar*C(O)-, Ar*C(O)NH-, Ar*NH-C(O)-, and (N-Ar*)(N-alkyl)N-C(O)-;

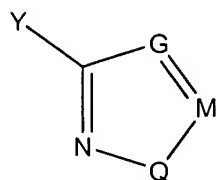
(2) R^h and Rⁱ where adjacent, together with their ring carbons form a C₅-C₇ fused cycloalkyl ring having up to two double bonds including the fused double bond of the Het group, which cycloalkyl ring can be substituted by one or more of the group consisting of alkyl-, alkoxyalkyl-, amino-, aminocarbonyl-, carboxy-, fluoro-, or oxo-substituents, except in the

case of alkyl, alkoxy carbonyl, and fluoro substituents, which can be located on the same or different carbon atoms;

- (3) R^h and R^i where adjacent, together with their ring carbons form a fused C_6 or C_{10} aryl ring;
- (4) R^h and R^i where adjacent, together with their ring carbons form a fused five to eight membered fused heterocycle, wherein the ring fusion is at a carbon-carbon bond of Het, wherein the fused heterocycle consists of ring atoms selected from the group consisting of carbon, nitrogen, oxygen, sulfur, or $S(O)_n$, wherein $S(O)_n$ is 1 or 2; or
- (5) R^h and R^i where adjacent, together with their ring carbons form a fused 5- or 6-membered heteroaryl ring containing at least one and up to three atoms of N for the 6-membered fused heteroaryl rings and from one to three atoms of N or one atom of O or S and zero to two atoms of N for the 5-membered fused heteroaryl rings.

Claim 4. (Cancelled)

Claim 5. (Presently Amended) The method of claim 3, wherein Het-Y is



wherein G is ~~N or~~ $C-R^h$;

M is ~~N or~~ $C-R^i$; and

Q is O, ~~S, or~~ $N-R^g$.

Claims 6-10. (Cancelled)

Claim 11. (New) The method of claim 5, wherein R^i is hydrogen and R^h is amino, Ar^* , acylamino, ureido, or thoureido.